Agency for Healthcare Research and Quality
Advancing Excellence in Health Care

NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Screening high-risk populations for lung cancer.

Bibliographic Source(s)

Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, Lewis N, Lung Cancer Screening Guideline Development Group. Screening high-risk populations for lung cancer. Toronto (ON): Cancer Care Ontario (CCO); 2013 Apr 18. 57 p. (Evidence-based series; no. 15-10). [89 references]

Guideline Status

This is the current release of the guideline.

The EVIDENCE-BASED SERIES report, initially the full original Guideline, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Main Recommendation

Recommendation 1

Screening for lung cancer with low-dose computed tomography (LDCT) is recommended in high-risk populations defined as persons 55 to 74 years of age with a minimum smoking history of ≥30 pack-years* who currently smoke or have quit within the past 15 years and are disease free at the time of screening.

*Pack-years = number of cigarette packs smoked per day x the number of years smoked.

Defining a Positive Result on LDCT and Follow-up of a Positive Result

Recommendation 2: Positive Result and Follow-up

- Screening modality: Screening for lung cancer should be done using an LDCT multidetector scanner with the following parameters: 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), with an average effective dose ≤1.5 millisieverts (mSv).
- Collimation should be ≤2.5 mm.
- Definition of a positive result: A nodule size of ≥5 mm found on LDCT indicates a positive result and warrants a 3-month follow-up CT. Nodules ≥15 mm should undergo immediate further diagnostic procedures to rule out definitive malignancy.
- Appropriate follow-up of a positive result: Follow-up CT of a nodule should be done at 3 months as a limited LDCT scan (i.e., only a slab covering the nodule will be scanned, not the entire chest). The Lung Cancer Diagnosis Pathway should be consulted for guidance on clinical work-up.

LDCT Screening Interval

Recommendation 3

Persons at high risk for lung cancer should commence screening with an initial LDCT scan followed by annual screens for 2 consecutive years, and then once every 2 years after each negative scan.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Lung cancer

Guideline Category

Risk Assessment

Screening

Technology Assessment

Clinical Specialty

Internal Medicine

Oncology

Preventive Medicine

Pulmonary Medicine

Radiology

Thoracic Surgery

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Respiratory Care Practitioners

Guideline Objective(s)

To determine the appropriate use, if any, of low-dose computed tomography (LDCT) in the screening of high-risk populations for lung cancer, including:

- Patient characteristics that define a high-risk population
- The necessary elements involved in defining a positive result on LDCT and follow-up of a positive result
- The appropriate screening interval
- Organized versus opportunistic screening

Target Population

Men and women considered at high risk for lung cancer based on their age and smoking history

Interventions and Practices Considered

Low-dose computed tomography (LDCT)

Major Outcomes Considered

- Lung cancer-specific mortality
- All-cause mortality
- Effect of low-dose computed tomography (LDCT) screening on smoking behaviour
- Potential harms of LDCT screening
- Effective settings

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Methods

The primary evidence base for this guideline is contained in a systematic review from a collaboration of the American Cancer Society, the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) (see the "Availability of Companion Documents" field). A clinical practice guideline was published in an online supplement to the systematic review and is available on the ASCO website. The collaborative systematic review was reviewed by a Research Coordinator from the Program in Evidence-based Care (PEBC) and the Working Group of the Lung Cancer Screening Guideline Development Group (see Appendix 1 in the original guideline document). The Working Group considered the collaborative review to be a comprehensive presentation of the current evidence on lung cancer screening in high-risk populations and employed it as the evidence base for this clinical practice guideline.

The search strategy from the collaborative systematic review was re-run in April 2013 to retrieve any relevant studies published since the previous search. The search was done in the MEDLINE and EMBASE databases using the identical search strategy of the previous search and covered the period from May 2012 to April 2013. The update search identified two relevant papers.

Methods of the Collaborative Review by Bach et al.

Literature Search Strategy

Searches were conducted using MEDLINE (1996 to 1 April 2012), EMBASE (1996 to April 2012), and the Cochrane Library (April 2012). References of relevant papers were reviewed for additional studies. The search strategy combined Medical Subject Heading (MeSH) and Emtree terms and related text words that described lung cancer, population screening, and low-dose computed tomography (LDCT). eAppendix 1 and eAppendix 3 in Bach et al. (see the "Availability of Companion Documents" field) describe the literature search strategy and study selection process.

Study Selection Criteria

Studies were eligible for inclusion if they were randomized controlled trials (RCTs) that compared LDCT screening with another form of screening or no screening, or were noncomparative studies in which all participants were screened with LDCT. Outcomes of lung cancer-specific mortality and all-cause mortality were only considered from RCTs. At least one of the following other outcomes of interest had to be included in the LDCT arm of RCTs or a single-arm study to be eligible: mortality from the evaluation of suspected lung cancer, the likelihood of nodule detection at initial screening test and/or at repeat screening, the frequency of invasive diagnostic procedures among those with suspected cancer, the frequency of follow-up imaging tests, and the rate of smoking cessation or smoking re-initiation.

Studies were excluded if the screening population had a primary risk factor other than smoking, if they were published in a language other than English, or if they reported outcomes only in patients diagnosed with lung cancer through screening.

Number of Source Documents

- A total of 21 studies (8 randomized controlled trials and 13 single-arm studies) were included in the review after initial search.
- Two more studies were included after the search update.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The primary evidence base for this guideline is contained in a systematic review from a collaboration of the American Cancer Society, the American College of Chest Physicians (ACCP), the American Society of Clinical Oncology (ASCO), and the National Comprehensive Cancer Network (NCCN) (see the "Availability of Companion Documents" field). The scores on the Assessment of Multiple Systematic Reviews (AMSTAR) tool for the collaborative systematic review are listed in Appendix 2 in the original guideline document, and the Appraisal of Guidelines Research and Evaluation (AGREE) II scores are in Appendix 3 in the original guideline document.

The risk-of-bias quality-criterion elements assessed by the systematic review were: appropriate question, reproducible methodology, adequate randomization, concealed allocation, sufficient sample size, comparable groups, blinding, validated and reliable measures, adequate follow-up, acceptable loss to follow-up, appropriate analyses, accurate results, and conflict of interest.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Formation of Guideline Development/Working Group

Cancer Care Ontario (CCO) Prevention and Cancer Control asked the Program in Evidence-based Care (PEBC) to develop a guideline on low-dose computed tomography (LDCT) screening for lung cancer. In consultation with Prevention and Cancer Control a Working Group was identified from the memberships of the Lung Cancer Disease Site Group (DSG), the Cancer Imaging Program, and Provincial Primary Care and Cancer Network. This Working Group consisted of a radiologist, a radiation oncologist, a respirologist, a thoracic surgeon, a primary care physician, and a methodologist. The Working Group and Prevention and Cancer Control also formed the Lung Cancer Screening Guideline Development Group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal Review

Almost all Program in Evidence-based Care (PEBC) documents undergo internal review. This review is conducted by the Expert Panel of the Lung Cancer Screening Guideline Development Group and the Report Approval Panel. The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Expert Panel for this document was comprised of members of the Lung Cancer Disease Site Group (DSG) and experts in the field of screening and population (see Appendix 1 of the original guideline document). The members of this group were required to submit conflict-of-interest declarations prior to reviewing the document. These declarations are described at the end of Section 2 of the original guideline document. The document must be approved by formal vote. In order to be approved, 75% of the Expert Panel membership must cast a vote or abstain, and of those that voted, 75% must approve the document. At the time of the voting, the Expert Panel members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval again.

A complete draft of the document was sent to the Expert Panel (11 members of the Lung Cancer DSG and three experts in screening or population health) on 3 August 2012 by email with instructions to review it and provide feedback.

Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making a final determination that the RAP's concerns have been addressed.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Lung Cancer Screening Guideline Development Group circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review

During the guideline development process, two targeted peer reviewers from Canada considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Two reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations, and whether the draft recommendations should be approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on January 31, 2013. Follow-up reminders were sent at 2 weeks (email) and at 4 weeks (telephone call). The Lung Cancer Screening Guideline Development Group reviewed the results of the survey.

Professional Consultation

Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. By searching the terms *screening*, *primary care*, *lung*, *thoracic*, or *imaging* in the PEBC database, clinicians likely to be interested in the guideline were identified and contacted by email to inform them of the survey. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1) and the evidentiary base (Section 2). The notification email was sent on February 13, 2013. The consultation period ended on March 19, 2013. The Lung Cancer Screening Guideline Development Group reviewed the results of the survey.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are supported by randomized controlled trials, systematic reviews, and single-arm studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Three of the randomized controlled trials (RCTs) reported data on the effect of low-dose computed tomography (LDCT) screening on lung

cancer specific mortality. The National Lung Screening Trial (NLST) was the largest (n=53,454) of the RCTs identified and included three annual rounds of screening and a median of 78 months of follow-up. Patients in the LDCT group had a 20% decrease in lung cancer-specific mortality compared with patients in the chest radiography (CXR) group (relative risk [RR] 0.80, 95% confidence interval [CI] 0.73 to 0.93, p=0.004). The number needed to screen (NNS) with LDCT to prevent one death from lung cancer was 320. The ongoing Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays (DANTE) and Danish Lung Cancer Screening Trial (DLCST) had much smaller sample sizes (n=2811 and n=4104, respectively) and compared five annual rounds of LDCT screening with usual care. At a median follow-up of 34 months, the DANTE trial showed a statistically nonsignificant decrease of 3% in lung cancer-specific mortality with LDCT compared with usual care (RR 0.97, 95% CI 0.71 to 1.32, p=0.84). The DLCST also reported no difference between groups (RR 1.15, 95% CI 0.83 to 1.61, p=0.43). A pooled analysis of the three trials provided a combined odds ratio of 0.82 (95% CI 0.72 to 0.94).

- All three trials also reported all-cause mortality. The NLST showed a statistically significant decrease in death from any cause with LDCT screening (RR 0.93, 95% CI 0.86 to 0.99, p=0.02), while the difference between groups in the DANTE trial (RR 0.97, 95% CI 0.80 to 1.20, p=0.84) and the DLCST (RR 1.19, 95% CI 1.01 to 1.40, p=0.059) was not statistically significant.
- The effect on smoking behaviour was examined in the systematic review because there is concern that a tendency exists with LDCT screening for smokers to continue smoking, and former smokers to return to smoking when screening results are negative. These concerns have been expressed previously in the literature. None of the studies in the systematic review addressed whether public statements regarding the benefits of LDCT affected smokers' behaviours. Of the few studies that examined quit rates or resumption of smoking rates, none showed significant changes in patients screened with LDCT. An analysis of the Early Lung Cancer Action Program (ELCAP) data examined whether consistently negative screening results are associated with less cessation and more relapse over a 6-year period, and found patients who received negative computed tomography (CT) scan results had a 28% lower likelihood of achieving point abstinence at one or more follow-ups than did those with a positive result. However, the study also found that a consistently negative result was not associated with a reduced long-term smoking abstinence or increased relapse back to smoking.

Potential Harms

- Potential harms of low-dose computed tomography (LDCT) screening identified in the systematic review included the high rate of noncancerous nodule detection (false-positive results) (90% to 97%), the frequency of repeat diagnostic imaging (2% to 58%) and invasive procedures (1.3% to 8% per screened individual), the risk for overdiagnosis (the detection of relatively indolent histologically confirmed lung tumours that would not have been detected or caused symptoms or disease during a patient's lifetime), which can have a negative effect on quality of life, and increased radiation exposure due to repeat scans required after the detection of an abnormality.
- The reporting of false-positive rates varied across studies, depending on the threshold described in a given study (0, ≥4, ≥5 mm) and the denominator used (all nodules over the threshold or all patients tested). Denominators were further affected by whether they were determined per screening round or per person year.
- In the National Lung Screening Trial (NLST), a positive screening-test result was defined as the detection of a noncalcified nodule measuring ≥4 mm in any diameter and that was deemed suspicious for lung cancer. The rate of a positive test result across the three screening rounds was 24% in the LDCT group compared with 6.9% in the CXR group. Diagnostic follow-up occurred for >90% of the positive test results, usually consisting of further imaging. Of the positive test results, 96.4% were false positive in the LDCT group and 94.5% were false positive in the chest radiography (CXR) group.
- The effective dose of radiation from LDCT was about 1.5 mSv per screen. In the NLST, the dose was about 8 mSv per participant over 3 years, including screening and diagnostic follow-up tests. From the NLST data, it was predicted that for every 2500 persons screened, 1 cancer death may be caused by radiation from imaging.
- The NLST was the only study to report on complications resulting from LDCT screening. The frequency per 10,000 persons screened of a major complication occurring during a diagnostic evaluation of a detected finding was 33 in the LDCT group and 10 in the CXR group. The frequency of death occurring within 60 days of a diagnostic evaluation of a detected finding was 8 per 10,000 persons screened with LDCT and 5 per 10,000 persons screened with CXR. Among the patients who had nodules detected by LDCT that were determined to be benign, death within 60 days occurred in 11 patients (0.06%), and major complications occurred in 61 patients (0.36%). Most of the major complications occurred after surgical procedures.

Qualifying Statements

Qualifying Statements

- Screening may be a reasonable option in persons with a smoking history of <30 pack-years. However, as this risk group was not included in the National Lung Screening Trial (NLST), an explicit recommendation in favour of screening such persons cannot be made at this time. A current trial (NELSON) includes patients with a minimum smoking history of 15 pack-years and may provide additional data to determine the minimum smoking history appropriate for screening.
- In the guideline development process, evidence from existing trials and guidelines from relevant organizations have been reviewed. Wherever possible, information collected has been applied to the Ontario environment. Where there are discrepancies in the literature (e.g., the definition of high risk), the panel arrived at a consensus. Where there is insufficient evidence in the literature (e.g., overall duration of screening), recommendations have been based on the Working Group's best judgement at the current time, and adjustments may be made when new evidence is available.
- Care has been taken in the preparation of the information contained in this report. Nonetheless, any person seeking to apply or consult the report is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. Cancer Care Ontario makes no representation or guarantees of any kind whatsoever regarding the report content or use or application and disclaims any responsibility for its application or use in any way.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Roberts H, Walker-Dilks C, Sivjee K, Ung Y, Yasufuku K, Hey A, Lewis N, Lung Cancer Screening Guideline Development Group. Screening high-risk populations for lung cancer. Toronto (ON): Cancer Care Ontario (CCO); 2013 Apr 18. 57 p. (Evidence-based series; no.

15-10). [89 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2013 Apr 18

Guideline Developer(s)

Program in Evidence-based Care - State/Local Government Agency [Non-U.S.]

Guideline Developer Comment

The Program in Evidence-based Care (PEBC) is a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

Source(s) of Funding

The Program in Evidence-based Care (PEBC) is a provincial initiative of Cancer Care Ontario supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC is editorially independent from the Ontario Ministry of Health and Long-Term Care.

Guideline Committee

Lung Cancer Screening Guideline Development Group

Composition of Group That Authored the Guideline

Working Group: Dr. Heidi Roberts, Medical Imaging, Women's College Hospital, Toronto, Ontario; Dr. Khalil Sivjee, Division of Respirology, Sunnybrook Health Sciences, Toronto, Ontario; Dr. Yee Ung, Radiation Oncology, Sunnybrook Health Sciences, Toronto, Ontario; Dr. Kazuhiro Yasufuku, Division of Thoracic Surgery, Toronto General Hospital, Toronto, Ontario; Dr. Amanda Hey, Regional Primary Care Lead, Hôpital régional de Sudbury Regional Hospital, Sudbury, Ontario; Ms. Cindy Walker-Dilks, Program in Evidence-based Care, McMaster University, Hamilton, Ontario; Dr. Nancy Lewis, Prevention and Cancer Control, Cancer Care Ontario

Expert Panel Members: Dr. Lawrence Paszat, Institute for Clinical Evaluative Sciences, Toronto, Ontario; Dr. Anthony Miller, Dalla Lana School of Public Health, University of Toronto; Dr. Linda Rabeneck, Prevention and Cancer Control, Cancer Care Ontario; Dr. Bill Evans, Lung Cancer DSG, Juravinski Cancer Centre, Hamilton; Dr. Swati Kulkarni, Lung Cancer DSG, Windsor Regional Cancer Centre; Dr. Andrew Robinson, Lung Cancer DSG, Sudbury Regional Hospital; Dr. Ronald Feld, Lung Cancer DSG, Princess Margaret Hospital, Toronto; Dr. Andrew Pearce, Lung Cancer DSG, Sudbury Regional Hospital; Dr. Conrad Falkson, Lung Cancer DSG, Cancer Centre of Southeastern Ontario, Kingston General Hospital; Dr. John Goffin, Lung Cancer DSG, Juravinski Cancer Centre, Hamilton; Dr. Richard Gregg, Lung Cancer DSG, Cancer Centre of Southeastern Ontario, Kingston General Hospital; Dr. Edward Yu. Lung Cancer DSG, London Regional Cancer Program; Dr. Peter Ellis, Lung Cancer DSG, Juravinski Cancer Centre, Hamilton; Dr. Natasha Leighl, Lung Cancer DSG, Princess Margaret Hospital, Toronto

Financial Disclosures/Conflicts of Interest

In accordance with the Program in Evidence-based Care (PEBC) Conflict of Interest (COI) Policy, the guideline authors, the provincial Lung Cancer Disease Site Group (DSG) and Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Four authors declared they had no conflicts of interest, and two (HR and KY) declared conflicts.

HR reported she was a principal investigator of the ELCAP study and the Pan-Canadian Lung Cancer Screening Study, and has given talks to community hospitals interested in lung cancer screening. Furthermore, her department is pursuing collaborations with third parties to perform lung cancer screening.

KY reported he has received educational and research grants from Olympus Medical Systems.

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.

Guideline Status

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Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario Web site.

Availability of Companion Documents

The following are available:

- Screening high-risk populations for lung cancer. Summary. Toronto (ON): Cancer Care Ontario (CCO); 2013 Apr 18. 5 p. Electronic copies: Available in Portable Document Format (PDF) from the Cancer Care Ontario (CCO) Web site.
- Bach PB, Mirkin JN, Oliver TK, Azzoli CG, Berry DA, Brawley OW, et al. Benefits and harms of CT screening for lung cancer: a systematic review. JAMA. 2012 ;307(22):2418-29. Electronic copies: Available in PDF from the Journal of the American Medical Association Web site.
- Program in evidence-based care handbook. Toronto (ON): Cancer Care Ontario (CCO); 2011. 15 p. Electronic copies: Available in PDF from the CCO Web site.

Patient Resources

None available

NGC Status

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